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MUSCLE RELAXANTS — I.

The first issue of The Medical Letter (1: 3, 1959) discussed meprobamate as a tranquilizer and promised a later appraisal of its usefulness as a muscle relaxant. Soon afterward a close chemical relation of meprobamate, carisoprodol (Soma — Wallace; Rela — Schering), joined the small group of drugs offered as muscle relaxants, and it was followed by a growing list of other new drugs claimed to be useful in relieving such symptoms as spasm, spasticity, rigidity and athetosis occurring in inflammatory, degenerative and traumatic disease of muscle, joints, discs, bursae, brain and spinal cord.

Since 1959, several appraisals of muscle relaxants have been drafted for The Medical Letter, only to be discarded after discussion with consultants. Most of the experts who were consulted considered the evidence of effectiveness unconvincing, but the editors were not ready to overlook the wide acceptance and use of these agents by physicians.

RELAXANT EFFECTS - As further evidence has accumulated, however, the doubts have been substantially resolved. Unlike curariform drugs, none of these drugs have specific blocking action on impulses at the neuromuscular junction; and it has not been shown that they have any direct effect on peripheral neuromuscular function. It now seems clear that any skeletal muscular effects achieved with these relaxant drugs, whether they are administered orally or parenterally, are similar to those obtained with barbiturates and tranquilizers. In a few controlled trials placebos have given much better results than some of the drugs. None of the drugs can of course be expected to reverse or control the disease causing the disordered muscle tone.

As with other therapeutic agents, the accumulating evidence of controlled clinical trials with muscle relaxants shows that neither favorable animal experiments, uncontrolled trials, nor wide acceptance by physicians can be relied upon to establish the value of a drug. Some oral drugs, whether or not offered as muscle relaxants, do have a relaxing effect, but the evidence indicates that this effect results not from any specific action on the muscles, but rather from their central-nervous-system-depressing sedative action. Thus the effectiveness of different barbiturates in reducing muscle spasm appears to be roughly proportional to their sedative or depressant effect on the central nervous system (F. E. Shideman, Clin. Pharm. and Therap., 2: 313, 1961).

Objective, quantitative measurements of muscle activity such as electromyography have been used to prove the effectiveness of various muscle relaxants. But muscle tone is influenced by emotions, mood and social setting; and anything that reduces tension, whether a sedative, the reassurance given by a physician, or a change in the patient's environment, may have a favorable effect. In the absence of controls, therefore, such measurements cannot establish the value of a drug in reducing spasm or spasticity.

COMPARISON WITH PLACEBO - In one of the few well-controlled trials of muscle-relaxant drugs (E. Denhoff and R. H. Holden, N. E. J. Med., 264:475, 1961), a standardized procedure has been maintained since 1955 in the evaluation of mephenesin, chlorpromazine, reserpine, zoxazolamine, carisoprodol and emylcamate for the treatment of spasticity associated with cerebral palsy. Each of these drugs has been matched with a placebo and comparisons made in groups of children studied for neuromuscular function as well as general behavior. Beneficial effects on neuromuscular function ranged from 9 per cent with reserpine to 56 per cent with mephenesin; the mean was 33 per cent. With placebo, the improvement varied from 26 to 50 per cent, and the mean was 39 per cent. Favorable effects on behavior ranged from 8 per cent with mephenesin to 53 per cent with zoxazolamine, with a mean of 37 per cent. With placebo, behavior ratings improved by 17 to 80 per cent, and the mean improvement was 46 per cent. The authors conclude that "placebo had a greater 'effectiveness' in each of the two rated categories."

EARLIER STUDY - The Denhoff-Holden study was not the first to cast doubt on the effectiveness of such drugs. In a review of muscle relaxants (Ann. N. Y. Acad. Sci., 67:833, 1957), Dr. Edward B. Schlesinger reported the results of fairly extensive experience in the treatment of a variety of acute and chronic disorders associated with increased muscle tone. He employed such drugs as barbiturates, quinine, trimethadione, diphenylhydantoin, promethazine, diethazine, caramiphen HCl, curare (tubocurarine), zoxazolamine, mephenesin, chlorpromazine, reserpine and meprobamate. "...regarding muscle spasm and spasticity," he concluded, "the quaternary ammonium salts, as exemplified by curare, are the only drugs with definite clinically recognizable direct effect. The substituted ethers of glycerol, as exemplified by mephenesin...have an unequivocal effect when given intravenously. These effects cannot be maintained practically for long periods by vein, and they cannot be obtained by oral administration...."

Intravenous — but not oral — administration of mephenesin (2% solution, at the rate of 1 cc. per minute to a maximum of 100 cc.), methocarbamol or phenyramidol does have a brief and variable effect in reducing muscle spasm associated with tetanus; it may also reduce muscle spasm sufficiently to aid in the reduction of dislocated joints. The antispasmodic effects apparently result from the sedative or tranquilizing action of the drugs on the brain and spinal cord; similar effects follow the use of parenteral barbiturates. As for the oral relaxant drugs, their wide acceptance must be credited to placebo effects much more than to specific pharmacologic effects.

(This appraisal of muscle relaxants will be concluded in an early issue of The Medical Letter.)

DULCOLAX

Bisacodyl (Dulcolax — Geigy) is promoted for use in both oral and suppository forms "whenever reliable and predictable bowel evacuation is required," as in acute and chronic constipation and preparation for sigmoidoscopy and barium radiography. The drug [bis(p-acetoxyphenyl)-2-pyridyl-methane] is not absorbed and has little or no effect in the small intestine; it acts by contact with the mucosa of the large intestine, where it stimulates contraction.

In the preparation of the bowel for barium roentgenography, the usual castor-oil-and-enema routine often causes excessive purging and cramps; several studies indicate that Dulcolax is a satisfactory and more acceptable substitute in many cases. One study (R. K. Keogh and R. G. Fraser, J. Assoc. Canad. Radiol., 9:66, 1958) compared the combined use of Dulcolax tablets and suppositories with the combination of castor oil and enema in preparing patients for barium contrast x-ray examination of the colon. Dulcolax gave "excellent" results more frequently than castor oil and enema, though the total of "excellent" and "adequate" results was about 95 per cent with both procedures. The patients on Dulcolax experienced less abdominal cramping and no diarrhea.

USE IN SIGMOIDOSCOPY - Many investigators have also reported the successful use of Dulcolax suppositories in the preparation of patients for sigmoidoscopy, but Medical Letter consultants find that the emptying of the sigmoid colon is sometimes incomplete. Because of the great advantage of the suppositories in convenience and acceptability, however, these consultants believe that Dulcolax deserves further trial in patients being prepared for sigmoidoscopy.

All of the studies with oral Dulcolax for the treatment of chronic constipation were uncontrolled, and the results were not impressive. The need for caution in assessing such studies is emphasized by a critical review of the methods of evaluation of laxative agents (not including Dulcolax) in constipated subjects (T. Greiner, et al., J. Chron. Dis., 6:244, 1957). In this study 14 of 20 patients with chronic constipation were able to go through an entire two-week period on placebo without resorting to pharmacologically active drugs.

Dulcolax suppositories, unlike the tablets, have been the subject of controlled as well as uncontrolled trials. In the rectal type of constipation, one or two Dulcolax suppositories (each 10 mg.) appeared to be more effective, much more convenient, and less irritating to the colon and rectum than water enemas or glycerin suppositories. Evacuation usually occurs about an hour after the introduction of one or two suppositories. In an uncontrolled study by D. A. Dreiling, et al. (Am. J. Dig. Dis., 4:311, 1959) of 19 patients with chronic constipation, 14 obtained satisfactory bowel movements with Dulcolax suppositories. In a double-blind trial (J. Levine and S. H. Rinzler, Am. J. Cardiol., 5:108, 1960), satisfactory bowel movements occurred in about 80 per cent of the 59 users of Dulcolax suppositories as compared with 42 per cent of the 50 users of glycerin suppositories.

TOXICITY AND SIDE EFFECTS - Experimental studies in animals and man have shown no absorption of the drug, and no systemic or allergic effects have yet been observed; but Dulcolax is too new to permit a final judgment of its safety.

Occasional abdominal cramps and tenesmus have been reported with both the oral and suppository forms of the drug. The suppositories appear to be less irritating than glycerin suppositories or water enemas.

In summary, the Dulcolax suppository appears to be a useful and convenient agent for the relief of rectal constipation, and it may be worth trying in the preparation of the terminal colon and rectum for sigmoidoscopy. The combination of oral and suppository Dulcolax is often an effective substitute for the traditional castor oil-enema routine in the preparation of the bowel for x-ray. There is no convincing evidence that oral Dulcolax is superior to other standard laxative agents for the relief of functional constipation. Dulcolax suppositories cost the patient about 40¢ to 50¢ each, the tablets (in quantities of 100) about 6¢ or 7¢.

TESTS OF DIGOXIN TABLETS

In tests of digoxin tablets performed for The Medical Letter, all but one of the samples of this cardiac drug purchased from 23 drug houses conformed fully to the requirements of the U.S. Pharmacopeia. In similar tests Digitoxin tablets USP fared less well, nearly a quarter of the samples being found substandard (Medical Letter, 3:47, June 9, 1961).

The substandard digoxin sample contained an excess of the drug (see table below). All of the samples (0.25 mg.) met the requirements for identification, disintegration time, and weight variation from tablet to tablet, and none contained as much of other digitoxosides as the maximum permissible amount, 4 per cent. One sample was purchased from each of the companies by pharmacists not connected with The Medical Letter and was sent to the laboratory for test identified only by code number. Except as noted, the variations are within the range permitted by the USP and are clinically not significant.

The following table shows the percentage of digoxin found, the percentage of other digitoxosides, and the price to the pharmacist for 1000 0.25-mg. tablets.

Company	Digoxin	Other	Price	Company	Digoxin	Other	Price
American Drug Prod.	105%	2.2%	$6.90	Nysco Labs.	*123%	1.3%	$4.50
American Pharm.	100	3.8	8.00	Penhurst Pharm.	101	3.0	5.95
Bryant Pharm.	99	2.4	5.95	Raway Pharm.	97	3.2	7.50
Burroughs Wellcome	102	2.3	8.40	Robinson Lab.	95	1.3	7.50
Columbia Medical	102	1.4	5.25	Stanley Drug	99	1.5	7.40
Robert Daniels	101	3.6	5.45	Success Chem.	105	1.5	7.00
Darby (Bio-Intrasol)	102	3.2	5.00	Supreme Pharm.	107	1.1	7.92
DuMont Pharm.	99	1.7	5.50	Vitarine	104	3.5	10.00
Jan Labs.	103	2.5	5.95	Wales (Winsale)	101	3.8	4.95
Lannett	102	2.0	8.00	West-ward	103	1.6	7.40
Lustgarten (Vitamix)	95	1.2	9.00	Wolins Pharm.	101	1.6	6.50
H. L. Moore	110	3.0	3.95				

*The Pharmacopeia permits a maximum of 110%

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